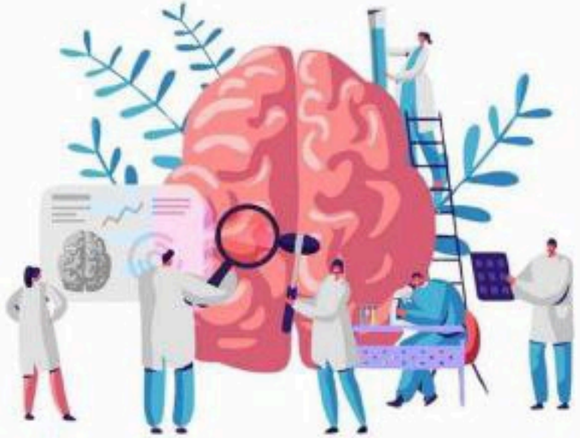


تفريغ لحاينتك

محاضرة: DOSAGE REGIMEN DESIGN

الصيدلاني\ة: Alaa Otoum

لجان الدُّفعات

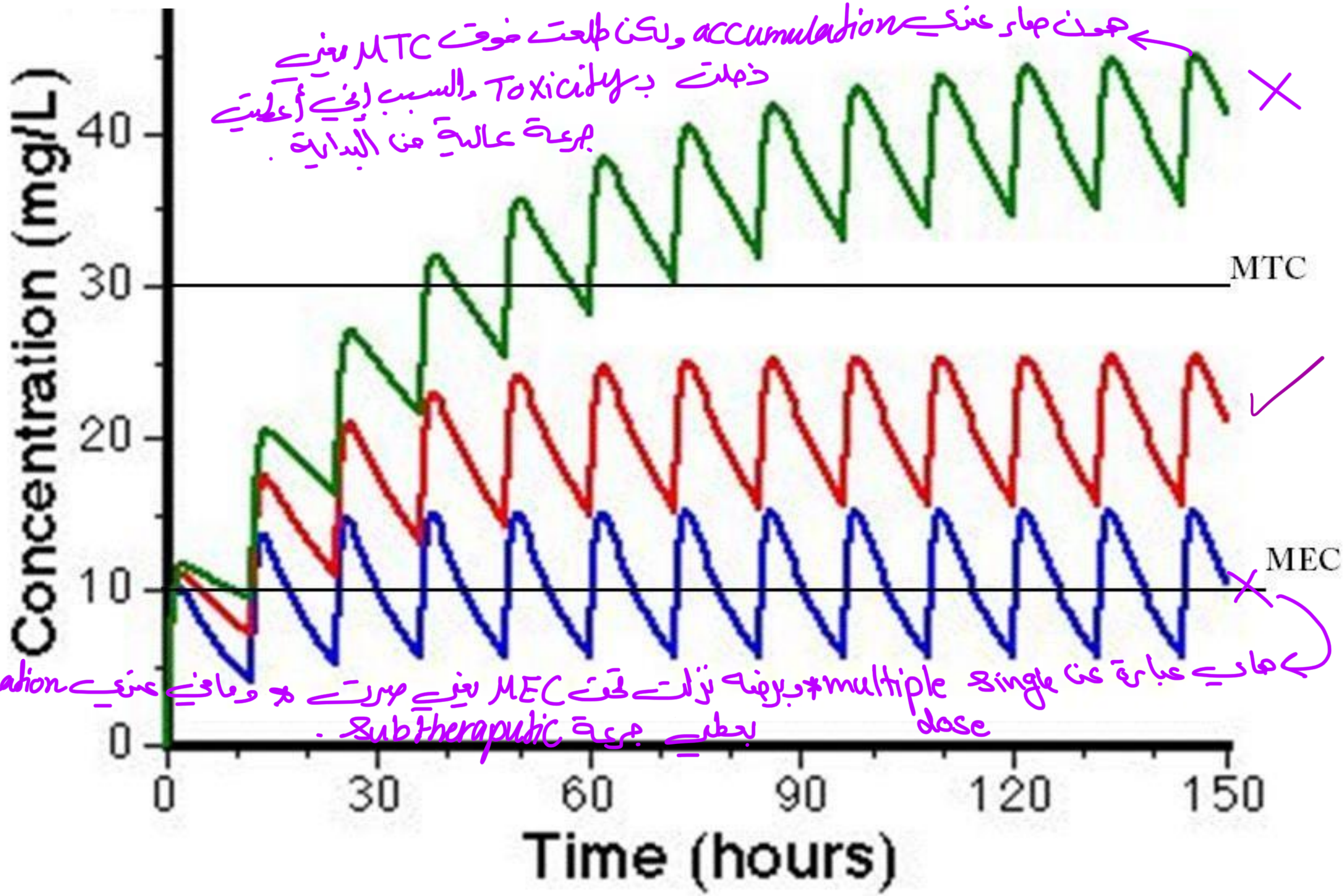
Soul Academy

Dosage regimen Design

طيب شو السبب إنه عنا الثلاث جرعات مختلفين؟ إما رح يكون السبب الـ frequency أو الـ dose لأنهم العاملين الرئيسين اللي بأثروا على الـ dose regimen

* وهون بما إنه الـ frequency ثابتة لهم الثلاث (10 hr) فأكيد السبب رح يكون

Dosage Regimen Design



هون هاي عنا accumulation ولكن طلعت فوق الـ MTC يعني دخلت بـ Toxicity والسبب إني أعطيت جرعة عالية من البداية.

هاي عبارة عن single multiple dose * بس هون نزلت تحت MEC يعني صرت بعطي جرعة subtherapuetic. * وما في عنا accumulation

OBJECTIVE OF DOSE REGIMEN DESIGN

- The objective is to maintain a minimum inhibitory concentration (MIC), or a minimum effective concentration (MEC) or to obtain a desired peak or a mean steady state concentration.
- Calculations are based on the equations on drug accumulation for multiple dosing with fixed dose sizes and fixed dosing intervals as discussed in

"Pharmacokinetics of Multiple Dosing."

INTRODUCTION- THERAPEUTIC RANGE

- In general, a therapeutic range should **never** be considered in absolute terms, as it represents no more than a combination of probability charts. In other words, a therapeutic range is a range of drug concentrations within which the *probability* of the desired clinical response is relatively high and the *probability* of unacceptable toxicity is relatively low.

- Moreover, with most drugs there are discrete **subpopulations** (because of disease, age, concurrent therapy, inheritance‘ and so forth) for whom concentration-effect relationships differ from the norm. the process of selecting the most appropriate dosage regimen to achieve concentrations in a relatively narrow range may be complicated by unpredictable intra-patient and inter-patient variability in the drug's pharmacokinetics.

Assumptions

- The equations for determination of dose sizes and dosing intervals are based on the open one-compartment model. Therefore, one must recognize the implications, assumptions, and limitations.

- It is assumed that all pharmacokinetic parameters remain constant during the course of therapy once a dosage regimen has been determined. In case one or more of the factors change, the once established dosage regimen is no longer valid.

يعني ما بنغير كل مرة أفضل أحسب
K أو Vd أو Cl للمريض

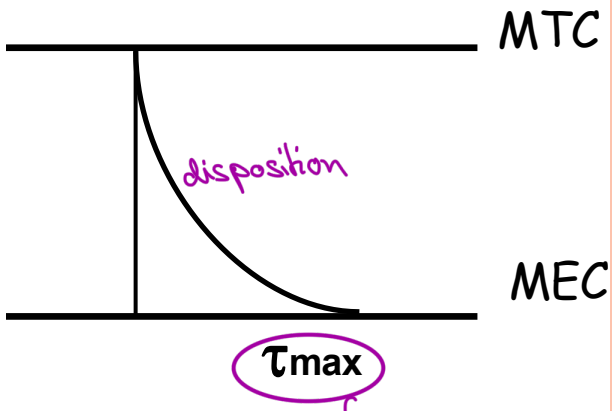
Factors influencing Dosage Regimen Design

The design of proper therapy depends on

- Pharmacokinetics of the drug: V_D, k, $t_{1/2}$, Cl
- Pharmacodynamic: therapeutic response and toxicity
- Biopharmaceutics: type of dosage forms and release profile of the drug (fast, sustained, …)
- Clinical state of the patient: any disease that affect renal and/or hepatic clearance or general health state of the patient
- Metabolism of drug: fast, slow metabolizing patients

Factors influencing Dosage Regimen Design

- For the time being we will focus on the following when designing dosage regimen:
  - Therapeutic index: Toxic level MTC /Minimum Effective level (MEC)
  - $t_{1/2}$ of the drug
- Drug level should be between MEC and MTC
- $t_{1/2}$ of the drug is used to determine the dosing interval (τ)



الـ time اللي بتاخد الدواء لحد ما ينزل من MTC إلى MEC

يعني لما أجي اعمل $\tau max = 8$ يعني أنا على 7.59 ثانية بكون لسا ما وصلت لـ MEC وإذا كانت 8.01 بكون نزلت تحت MEC وصار الدواء subtherapuic . بالتالي الـ τmax أنا ما لازم أنزل تحتها لازم أكون قبلها .

Protocols for Pharmacokinetic-Guided Dosing Regimens

- Clinically, it may be necessary to apply pharmacokinetic principles to determine dosing regimens for individual patients when one or more of the following criteria are met:
- A drug has a narrow therapeutic range, and plasma concentrations are outside the range are associated with serious clinical consequences.
- A drug displays wide interpatient variability in its pharmacokinetic parameters.
- A patient possesses a characteristic that is frequently associated with altered pharmacokinetics. This may include renal disease, hepatic disease, altered activity of the drug metabolizing enzymes or transporters as a result of genetic polymorphism or concomitant medications.

Protocols for Pharmacokinetic-Guided Dosing Regimens

- Steady state can be reached by giving a loading dose and/or by multiple dose (after certain time)
- We have three protocols for designing a proper dose regimen
  - By maintaining the same average concentration at SS (Cssav)
  - By maintaining the same maximum concentration at SS (Cssmax)
  - By maintaining the same minimum concentration at SS (Cssmin)

عشان أعمل dose regimen لازم أثبت واحدة من هدول التلاتة ويكون 99% من الأدوية بثبت الـ Cavg.

ويكن في حالات بدي أثبت الـ Cmax دون Cmin متى ؟!

Cmax

في عندي أنواع anti biotic بدي أثبت الـ Cmax اسمهم dose dependent صح بدي يكون الـ Con كبير عالي عشان أعمل Killing للبكتيريا ذ بدي Cmax عالية ولكن بنفس الوقت لازم أثبتها تحت الـ toxicity.

Cmin

في عندي أنواع anti biotic اسمهم time dependent يعني مش كبير بدي الـ Conc بس بدي يكون ضمن الـ therapudic range ذ مش كبير بدي الـ Conc المرجو أكون فوق الـ MEC

هذا الحكي كله مشروح بسلايد 21 & 24

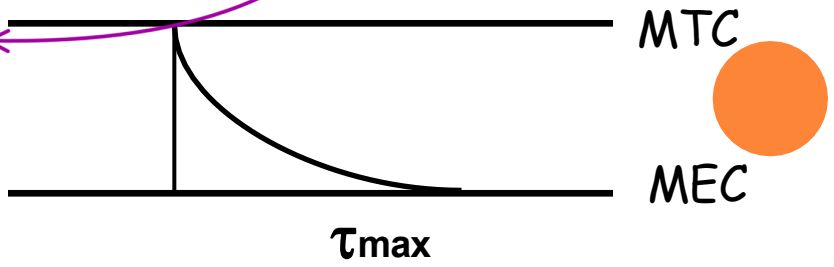
Dosage Regimen Design, Maintaining the same average concentration at SS (C_{SSAV}) based on fixed Cmax and Cmin

i.v. one compartment multiple dosing regimen design

- First, MTC and MEC for the drug should be known
- Then, the time needed for the concentration to drop from MTC to MEC is determined; i.e. Maximum dosing interval (**τ**)

- If we exceed (**τ**), therapeutic failure happens so we'll call it τ_{max}

- τ_{max} is defined as the maximum dosing interval after which the concentration falls below the MEC



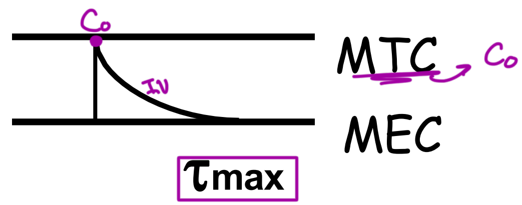
Dosage Regimen Design, Maintaining the same average concentration at SS (C_{ssav}) based on fixed Cmax and Cmin

① calculate of τ_{max} Theoretical → calculate τ_{max} practical: 5 steps الـ عشان أصمم dose regimen أنا لازم أعمل

② calculate $C_{avg(ss)}$ ③ calculate of dose interval ④ calculate dose ⑤ calculate R of $C_{max(ss)}$ & $C_{min(ss)}$

i.v. one compartment multiple dosing regimen design

$$MEC = MTC * e^{-k\tau_{max}}$$



$$\frac{MEC}{MTC} = e^{-k\tau_{max}}$$

$$\ln\frac{MEC}{MTC} = -k\tau_{max}$$

Therapeutic index (TI) = MTC/MEC

$$-\ln TI = -k\tau_{max}$$

$$\tau_{max\ (Theoretical)} = \frac{\ln TI}{k}$$

$$\tau_{max} = 1.44 * t_{1/2} * \ln TI$$

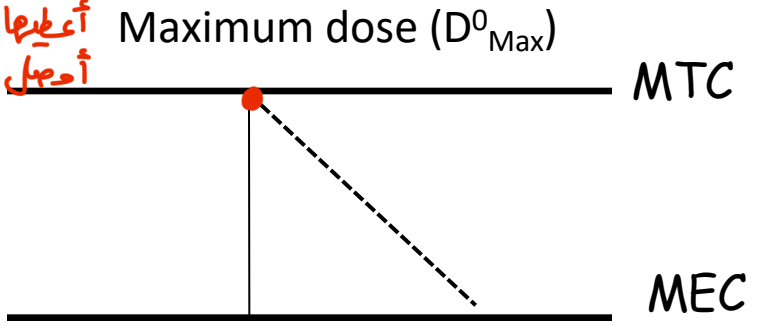
كم بس تطلع معي بقربها لمضاعفات الـ 24 (τ_{max} practical)

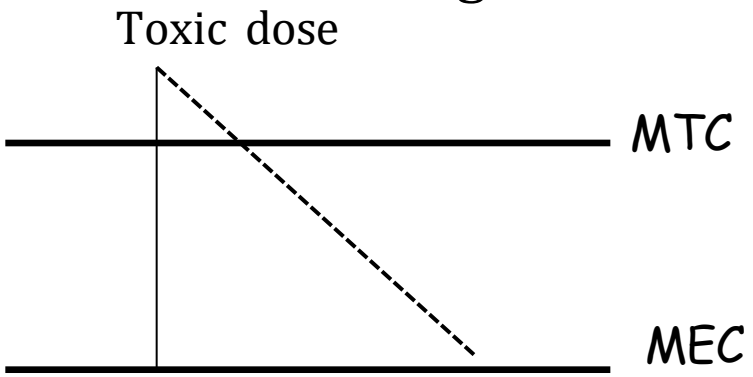
Dosage Regimen Design, Maintaining the same average concentration at SS (C_{ssav}) based on fixed Cmax and Cmin

i.v. one compartment multiple dosing regimen design

Determination of the maximum maintenance dose (X^0_{max}), that can be given without reaching the MTC

أعلى جرعة تقدر أعطيها بدون ما أوصل MTC





(X^0_{Max}) Maximum (effective) maintenance dose =(MTC-MEC)*V_D

In practice, X^0_{Max} **and** τ_{max} are determined at the beginning of dosing regimen and the values that used clinically are lower to avoid toxicity or therapeutic failure but result in **same Cssav**

Dosage Regimen Design, Maintaining the same average concentration at SS (C_{ssav}) based on fixed Cmax and Cmin

i.v. one compartment multiple dosing regimen design

X^0_{Max} when administered every τ_{max}, it will produce an average concentration during that dosing interval

$$C_{ss(av)} = \frac{X^0_{max}}{Cl * \tau_{max}}$$

$$X^0_{max} = C_{ss(av)} Cl * \tau_{max}$$

$$X^0_{max} = (MTC - MEC) * V_D$$

Thus, Cssav can be determined from TI:

$$C_{ss(av)} = \frac{MTC - MEC}{\ln(MTC/MEC)} = \frac{MTC - MEC}{\ln TI}$$

Dosage Regimen Design, Maintaining the same average concentration at SS (C_{ssav}) based on fixed Cmax and Cmin----STEP BY STEP

1) Estimate the desired (target) average steady state concentration

$$C_{ss(av)} = \frac{MTC - MEC}{\ln(MTC / MEC)}$$

2) Estimate the maximum allowable τ max

$$\tau_{max} = 1.44 * t_{1/2} * \ln TI$$

TI= MTC/MEC

$$\tau_{max} = \frac{\ln TI}{k}$$

Dosage Regimen Design, Maintaining the same average concentration at SS (C_{ssav}) based on fixed Cmax and Cmin----STEP BY STEP

3) Chose a practical τ based on the calculated τmax (e.g. 6,8,12,24 hrs)

4) Calculate the dosing rate (Xo/τ)

$$C_{ss(av)} = \frac{X^0}{Cl * \tau}$$

Dosing rate= $Cl * Css_{avg}$

↳ dose interval

Dosage Regimen Design, Maintaining the same average concentration at SS (C_{ssav}) based on fixed Cmax and Cmin----

STEP BY STEP

5) Calculate appropriate dose from dosing rate (step 4) and practical τ (step 3)
   Dose= dosing rate*τ
6) Re-calculate Css (max, min, avg) using the practical dosing interval and the chosen dose.
   To recalculate Cmaxss and Cminss you need first to calculate R

EXAMPLE 1

- Drug X has the following characteristics:
- Cl= 3.2 L/hr, Vd=35L, elimination half life 7.6hr F=1, TI=10-20 mg/L. Design a practical dosage regimen for drug X after intravenous administration based the values of TI

$\frac{0.693}{7.6} = 0.0924$

عشان بال 5 steps اللي حكينا عنهم .

① $\tau_{max} = \frac{\ln TI}{k} = \frac{\ln \frac{20}{10}}{0.0924} = 7.5\ hrs$ → Theoretical ⇝ τ_{max} practical $= 6\ hr$

بصيرة 8 بس عشان ما أغير ال dose 6 أسهل .

② $C_{avg(ss)} = \frac{MTC - MEC}{\ln TI} = \frac{20-10}{\ln 2} = 14.4$

خفت ال Theraputic range يعني لحد الآن ماشي تمام

③ dose interval $= cl * C_{avg} = 3.2 * 14.4 = 46.1\ mg/hr$

قللتها عشان بالعادة ما في عنا مواد جرعته 276 ودايما بتقرب للأقل عشان آمن .

④ dose = dose interval * τ_{max} practical $= 46.1 * 6 = 276.6\ mg \simeq 270\ mg$

⑤ $R = \frac{1}{1 - e^{-k\tau_{max\ practical}}} = 2.35$ (τ = 6)

$C_{max} = C_0 R = \frac{dose}{Vd} R = \frac{270}{35} * 2.35 = 18.05\ mg/L$

$C_{min} = C_0 R e^{-k\tau_{max\ practical}} = 18.05 * e^{-0.0924 * 6} = 10.36\ mg$

EXAMPLE 1

1) Css avg= $\boxed{\frac{20-10}{\ln(20/10)}} = 14.4\text{mg/L}$

2) $\tau\text{max} = \boxed{\frac{\ln(20/10)}{0.091}} = 7.6 \text{ hrs}$

3) A practical τ would be 6 hrs

4) Dosing rate (Xo/τ)= Cssavg*CL=14.4*3.2=46 mg/hr

5) Dose= dosing rate*τ=46*6=276 (round the number to the nearest available commercial strength of the drug e.g. 275mg)

EXAMPLE 1

- If we re-calculate Cmaxss, Cminss and Cavgss, the following values will be obtained
- Cavgss= 14.4 mg/L
- R=2.4
- Cmaxss=18.9 mg/L
- Cminss=11 mg/L; so they are with in the required range
- If a loading dose is required then $D_L = R * D_M$
- Loading dose=275*2.4=660 mg

Dosage Regimen Design, Maintaining the same $C_{SS(MAX)}$

- It is important to maintain maximum concentration (Cssmax) for some drugs.
- For instance, the killing activity of some antibiotics (dose dependent) depends on the drug's maximum concentration so by increasing the concentration of the drug, efficacy of killing the bacteria increased exponentially.
- So whenever we give a dose, we need to get a certain Cssmax
- Thus all calculations are based on Cssmax

Dosage Regimen Design, Maintaining the same $C_{SS(MAX)}$

1) Find the maximum τ max as explained in the previous slides
2) Find practical τ , which should be less than τmax and use it in calculations of the dose
3) From the Cssmax equation (CSS(Max) is determined from MTC) calculate the required dose based on the practical tau

$$C_{ss(max)} = C^{0} * R$$

$$C_{ss(max)} = \frac{X^{0}}{V_D} * \frac{1}{1 - e^{-k\tau}}$$

$$X^{0} = C_{ss(max)} * V_D \left(1 - e^{-k\tau}\right)$$

Dosage Regimen Design, Maintaining the same $C_{SS(MAX)}$

- REMEMBER to recalculate the Cmaxss using the chosen dose and dosing interval and decide if your regimen is suitable

* طيب حسب أنا إذا طلع معي الdose 948 هل بعتبرها Cmax ؟ 945 و 950

في حالة الCmax زي مكنيا جاي الشايب (antibiotic dose dependent) مكنيا عادي أنا مابهمني وإذا رفعت الdose بس المهم ما أوصل الtoxicity. بالتالي الـ 948 رح اعتبرها 945.

Dosage Regimen Design, Maintaining the same $C_{SS(MIN)}$

- In this approach, the concentration should be kept above certain concentration

شو ما طلعت مع الdose برفعها يعني Cmin
لو طلعت 948 هل بنزل 945 ولا بطلع لـ 950 ؟
لا بطلع لـ 950.

- Some antibiotics are called **time dependent** so we have to keep the concentration above MIC like sulfonamides
- In designing any dosage regimen this means that we have to fix the Cssmin
- The design the regimen based on Cssmin, the same steps explained in the previous slides ,however the dose is calculated from Cmin

Dosage Regimen Design, Maintaining the same $C_{SS(MIN)}$

$$C_{ss(\min)} = C^{0} * R * e^{-k\tau_{max}}$$

$$C_{ss(\min)} = \frac{X^{0}}{V_D} * \frac{1}{1 - e^{-k\tau_{max}}} * e^{-k\tau_{max}}$$

$$D^{0} = \frac{C_{ss(\min)} * V_D \left(1 - e^{-k\tau_{max}}\right)}{e^{-k\tau_{max}}}$$

DOSAGE REGIMEN DESIGN, EXTRAVASCULAR ADMINISTRATION

dose regimen oral اصعب كي بالامتحان طالع يجي أبدًا لأنه حساباته معقدة فرع يجي بس IV .

- Designing dosage regimens after oral administration is more complex than after intravenous administration.
- One extreme case that simplifies calculations is when Ka is large thus the duration of the absorption phase is short (SHORTER THAN SIXTH the half life), absorption is rapid and instantaneous, in such case the previous intravenous equations apply for extravascular administration but F needs to be accounted for.

$$\tau_{max} = \frac{\ln TI}{k} + t_{max}$$

Dosage Regimen Design, extravascular administration

Oral one compartment multiple dosing regimen design

X^0 when administered every τ_{max}, it will produce an average concentration during that dosing interval

$$C_{ss(av)} = \frac{F X^0}{Cl * \tau_{max}}$$

Dosage Regimen Design, Example

- An antibiotic is used intravenously to treat lower respiratory tract infections has elimination rate constant = 0.16/hr, volume of distribution =10 L, and therapeutic window between 10 and 100 mg/L. Design a dosage regimen for optimum efficacy, based on:
  - Average concentration at steady state
  - Maximum concentration
  - Minimum concentration

SOLUTION

Based on Css average

- τmax = ln (100/10)/0.16 ➔ 14.4 h ➔ Practical τ is 12h
- Css avg➔ 39.1mg/L $\frac{MTC-MEC}{\ln T1} = \frac{100-10}{\ln 10}$
- Dosing rate=Cssavg*CL➔39.1*0.16*10➔62.56mg/h (0.16 = K, 10 = Vd)
- Dose=62.25*12=750.7 mg ➔750 mg twice daily (12 = τ max practical)
- **Recalculate Cssmax and Cssmin to ensure you are in the therapeutic range** $R = \frac{1}{1-e^{-K\tau_{max}}} = \frac{1}{1-e^{-0.11*12}} = 1.17$
- Cssmax=(750/10)*R(1.17)➔87.75mg/L (750 = dose, 10 = Vd)
- Cssmin= Cssmax*$e^{-K\tau}$ ➔12.86 mg/L

therapeutic range

Based on Cssmax and Cssmin

- Css(max)=C_0*R➔ 100
  X_0=(Cssmax*VD)/R➔100*10/1.17=854.7➔860 mg twice daily

- Cssmin= Css(max)*R*$e^{-K\tau}$ ➔
  X_0=(Cssmin*VD)/(R*$e^{-K\tau}$)➔ 582 ➔600 mg twice daily
  (0.16, 12, 10)

- Remember that calculation were based on practical τ of 12 h calculated earlier.

- Remember to double check the final concentrations after approximation of doses